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THE PATENT OFFICE OF THE GERMAN FEDERAL REPUBLIC

DISCLOSURE SPECIFICATION

DE 39 22 441 A 1

Ref.:	P 39 22 441.4	Int. Cl. 5: A 61 K 31/19 A 61 K 31/195
Date of application:	7.7.89	
Date of disclosure:	17.1.91	

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Ibuprofen- and S-(+)-ibuprofen preparations and a process for their production

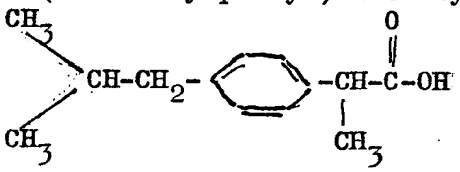
The invention concerns a preparation with improved tablettability containing ibuprofen and/or S-(+)-ibuprofen as well as conventional drug additives and/or vehicles whose characteristic is that it contains the calcium ibuprofen salt and/or the calcium-S-(+)-ibuprofen salt, and also a process for its production.

Page 2
Column 1

Description

The invention concerns a preparation with improved tablettability, greater hardness and wider melting range that contains ibuprofen or S-(+)-ibuprofen and conventional additives and/or drug vehicles, and a process for its production.

Ibuprofen (INN) of the following formula (I) is a racemate from D-(-)- and L-(+)-2-(4-isobutylphenyl)-isobutylphenyl propionic acid.



(I)

The form effective therapeutically is the laevorotatory L-(+)-2-(4-isobutylphenyl)-isobutylphenyl propionic acid and/or the L-(+)-ibuprofen whilst the dextrorotatory D-(-)-ibuprofen is practically ineffective. As in the organism the racemate is being converted enzymatically into the effective L-form in principle it is not wrong to use the stereo-isomer mixture as the drug substance. However, the L-(+)-ibuprofen has a greater and speedier efficacy so that it can be used in smaller doses (see S.J. Hutt and J. Caldwell; Review: The metabolic chiral inversion of 2-arylpropionic acids - a novel route with pharmacological consequences, J. Pharm. Pharmacol. 35, 693-704 (1983)).

In therapy ibuprofen and L-(+)-ibuprofen are being used as steroid-free antirheumatics antiarthritics or analgesics.

Technologically both these substances have the following disadvantages: They are only slightly soluble in water and have relatively low melting temperatures. Ibuprofen melts at 75 to 77°C and L-(+)-ibuprofen lower still at about 48 to 51°C. As is known, in tablet compression substances with low melting points are causing more or less marked production problems due to sinter processes and through adhesion to the punches and dies of the tabletting press (H. Sucker, P. Fuchs and P. Speiser: Pharmazeutische Technologie, Georg Thieme Verlag, Stuttgart 1978, p. 381).

The adhesion of these substances of low melting point can be overcome by overdoses of anti-adhesion agents (mold separators). In this, however, the mixtures are being made hydrophobic. This in turn results in a poor bioavailability or in tablets that are too soft on account of excessive anti-adhesion agent.

Up to a certain degree the complications in tabletting can be overcome by adding larger doses of additives such as anti-adhesion agents and/or lubricants or by a drastic reduction of the compressing speed. Moreover, it is known from experience that in the case of tablets containing ingredients of low melting point one will have to expect an after-hardening after certain storage periods that is due to sintering (K.H. Bauer, K.H. Froemming and C. Fuehrer: Pharmazeutische Technologie, Georg Thieme Verlag, Stuttgart, New York, 1986). This after-hardening leads to a
Column 2 poorer decomposition time and, consequently, an inadequate drug release and/or inadequate bioavailability.

With changeable results it has so far been tried to overcome these disadvantages by adding mold-separators or lubricants, siccatives (such as highly disperse silicic acid), suitable fillers and strong decomposition accelerators (such as cross-linked PVP), above all, however, by above average increases of the quantities of these added adjuncts.

EP-A-02 67 321 describes a pharmaceutical containing ibuprofen in only the S-(+)-form. But this known product does have the above disadvantages, i.e. it is difficult to compress into tablets.

The sintering or melting together can be reduced by adding fairly large quantities of filler material, for instance cellulose powder or lactose, or by disintegrants such as starch. Too large quantities of the latter, however, usually results in too soft tablets as starch or other substances of similar elasticity alone or in large quantities are difficult to compress, or the tablets are becoming so large that they are difficult to swallow.

The present invention set out to provide a preparation containing ibuprofen or S-(+)-ibuprofen that was to have an improved tablettability, a greater hardness and increased melting point, and a process for its production. The tablets were to be of a size that could be swallowed easily. The aim was particularly to provide a material that could be made into tablets easily and that would not adhere to the punches and dies of the tabletting machines so that in tabletting production problems would not occur. The preparation as well as the products made from it, tablets, capsules etc., were to have an adequate shelf-life. The invention was to provide a preparation that would ensure an adequate bioavailability even after a certain period of storage.

It has now been found that the above problems in the production of the tablet granulates can be avoided easily by converting ibuprofen or L-(+)-ibuprofen wholly or partially into their calcium salts and by using these for tabletting. Already 25% of the calcium salt of ibuprofen will improve the tabletting properties noticeably; preferred are 50 to 100%, i.e. the use of half or all the ibuprofen in form of the calcium salt. It is preferred, furthermore, that in executing the usual mixing or fluidized bed granulating operations what should be used as granulating liquid are alkali- or ammoniumhydroxide- or salt solutions.

The object of the invention is a preparation with improved tablettability that contains ibuprofen and/or S-(+)-ibuprofen as well as conventional additives and/or vehicles and the characteristic of which is that it contains the calcium ibuprofen salt and/or the calcium-S-(+)-ibuprofen salt.

A preferred preparation under the invention additionally contains at least one compound of the group sodium, potassium, ammonium ibuprofen salt, sodium, potassium, ammonium-S-(+)-ibuprofen salt, ibuprofen and S-(+)-ibuprofen.

column 3 The object of the invention is also a process for the production of the above preparation the characteristic of which is that ibuprofen or S-(+)-ibuprofen or a mix of these compounds, possibly with conventional additives and/or vehicles, are treated with a solution or suspension of calcium oxide, calcium hydroxide, potassium hydroxide, ammonium hydroxide, sodium carbonate, sodium bicarbonate or ammonium bicarbonate, that where necessary vehicles and/or additives are incorporated, that the mixture obtained is granulated in a way known as such, is dried where applicable and - possibly after adding further adjuncts and/or vehicles - is made, in a way known as such, into a form suitable for oral administration.

Under the invention the ibuprofen and/or the S-(+)-ibuprofen is converted into the calcium salt. The calcium salt is produced in a way known as such. In the calcium salt the calcium and the base do not have to be present in stoichiometric proportions The acids can be present in a stoichiometric excess.

A preferred version of the invention contains the calcium salt with additional alkali or ammonium salt. Used under the invention are the alkali or ammonium salts, preferably the carbonates or the hydrogen carbonates. The preferred alkali salts or hydroxides are the sodium, potassium salts or hydroxides. Examples of such salts and hydroxides are sodium carbonate, sodium hydrogen carbonate, potassium carbonate, potassium hydrogen carbonate, ammonium carbonate, sodium hydroxide, potassium hydroxide, ammonium hydroxide and ammonium bicarbonate. To be used as the calcium compound in the invented process may be the calcium hydroxide, calcium oxide and calcium carbonate. Of these the ammonium hydroxide, potassium hydroxide and calcium hydroxide are preferred particularly.

The ibuprofen calcium salts are the basic salts present in the product under the invention, and due to them the melting range is forced up unexpectedly and the tablettability is thus improved. Depending on proportions, the ammonium and the alkali salts are improving the solubility and are thus controlling the bioavailability. But they do again increase the hygroscopicity and also the stickiness.

The alkali-, alkaline earth- or ammonium salts or hydroxides are used in such quantities that - related to the ibuprofen - they are present in 25 to 110% of the equivalent quantity.

They do not necessarily have to be 100% equivalent. Only 25% of the computed equivalence can be adequate, but preferably 40 to 100% are sufficient. But not be used should be additional quanties of these bases or salts that would exceed the computed equivalent quantities by more than 10% (total < 110%). For in such cases the reaction of the aqueous solutions or suspensions of the products obtained will become too alkaline.

Under the invention it is preferred to use the additives in form of an aqueous solution, the concentration of the aqueous solution depending on the solubility of the additives. What may also be used in the case of additives of poor solubility Column 4 are suspensions of the deposits. The quantity of the solution or suspension depends

on the quantity of liquid required for granulation, and any expert can establish this easily. Where the additives are dissolved completely they react faster, the undissolved ones do not react so that in that case the result is a substance mix.

What is meant by the solutions or suspensions of alkali-, alkaline earth- or ammonium hydroxides, carbonates or hydrogen carbonates adjusted in a certain way are preferably preparations and/or granulation liquids. It is preferred that the quantity of additive should be related or adjusted to ibuprofen.

The solubility of the products obtained in this way can also be controlled by the salt formation. For whilst the alkali- and ammonium salts of ibuprofen are freely soluble in water the calcium salt is less freely soluble. Through specific mixing of salifying agents resulting in salts of better or poorer solubility the solubilities and/or dissolution speeds of the resulting products can be controlled to a certain extent. The control of the solubilities also controls the bioavailability. Ibuprofen calcium salt is less well soluble, less hygroscopic, but it can be tabletted and granulated better through increasing the melting temperature and hygroscopicity.

It should be taken into account that the 100% alkali salts (Na and K) do not only react much more alkaline but are also very hygroscopic. It is therefore less advisable to use a 100% equivalent and/or to use solely alkali hydroxides or salts as salifying agents. A partial neutralisation through adding a sub-equivalent quantity of alkali hydroxides or carbonates to ibuprofen or L-(+)-ibuprofen can already buffer sufficiently, as already mentioned. Preferred is the formation of mixed salts from alkali hydroxides or salts, ammonium hydroxide or salts with calcium hydroxide or carbonates and the ibuprofens.

Under one of the preferred versions of the invention the preparations are containing up to 40%w, related to the ibuprofen, of a lower neutral or acid amino acid. For instance, ibuprofen preparations that can be tabletted well are obtained where ibuprofen or L-(+)-ibuprofen is treated with buffer solutions from a lower amino acid and alkali-, alkaline earth- or ammonium hydroxides or salts as granulating liquid using mixers or in a fluidised bed. Examples of lower amino acids are glycin, alanine, valine, aspartic acid, glutamic acid, proline or hydroxyproline. The amino acid quantity may amount to up to 60%w, related to the ibuprofen. Preferably it should amount to 15 to 60%w, particularly preferred is 30 to 40%w.

An additional buffering, particularly of the stronger bases such as NaOH and KOH, can thus be brought about by adding neutral or acid amino acids. Ibuprofen acid easily reacts with alkaline amino acids like lysine but not with neutral or acid amino acids. For instance, ibuprofen does not or hardly react with glycine (amino acetic acid) or similar neutral or acid amino acids. But where the Na-, K-, NH_4- or Ca-salts of glycine or similar amino acids have been formed previously these can react well with ibuprofen, there then coming about a mixed salt formation. Created
Column 5 are well-buffered mixtures or complexes. In adding calcium the solubility of the resulting products is not always adequate.

The alkali-, alkaline earth- or ammonium hydroxides or salts are used in the same quantities as described above under the preparations without amino acids as a buffer.

In the production of these granulating liquids the glycine or another amino acid is first mixed with alkali-, alkaline earth- or ammonium hydroxide or salt or mixtures thereof and dissolved in water. With this solution ibuprofen or L-(+)-ibuprofen is then granulated in the same way as (above) the preparations without amino acid buffer and it is dried carefully.

The described mixing and fluidised bed granulating processes in which the resulting more or less salt-like ibuprofen products can also be drawn upon suitable vehicles like cellulose powder, micro-crystalline cellulose or mannitol to achieve a favourable dispersion, so changes the structure that after adding the usual tabletti adjuncts such as decomposition accelerators and lubricants these products can be compressed into tablets much more rationally and with fewer difficulties.

The products under the invention surprisingly have improved tabletting properties, especially as regards stickiness, hygroscopicity and melting properties. The improved tabletting properties are obviously brought about by the increase of the melting range temperatures due to complete or partial salt formation during the granulating process, depending on the type and the quantity of the alkalis or their carbonates used.

Through the admixture of alkali- and/or NH_4-hydroxides or salts the solubilities and thus the bioavailabilities are being improved considerably. Apart from improved tabletting properties and the dissolution speed of the ibuprofens being controlled in a certain way (drug release/bioavailability), to these buffered preparations can also be attributed an improved tolerance, as is known from "buffered aspirin". Acetylsalicylic acid can irritate the mucosa, and this phenomenon can be reduced by added buffers (W. Hangarter: Salicylic acid and its derivatives, F.K. Schattauer Verlag, Stuttgart, New York, 1974, p. 354/355).

The preparations under the invention are available in a form suitable for oral intake, for instance in form of tablets, coated pills, coated tablets, capsules, granules or in form of tablets, coated pills, coated tablets, capsules, granules with retard effect. For the production of preparations with sustained active substance release it is preferred to use the pure calcium salts, i.e. without added alkali- or ammonium salts, where required together with the usual retarding additives or adjuncts such as hydrogenated caster oil or carboxymethyl cellulose. This will retard the bioavailability in a certain manner. It is possible to incorporate the pure or separately produced ibuprofen salts into the preparation or to make the preparations in such a way that the salts are created in doing so. Suitable drug preparations are particularly the solid ones such as granulates, pellets, tablets, coated tablets and pills (film- or sugar coated) and capsules. Depending on the desired speed of release and/or dissolution of the preparation, used as the salt mixture are certain proportions of soluble and insoluble salts or salts that are easily or not easily soluble. As mentioned above, the salts are created through the reaction of ibuprofen with CaO, $Ca(OH)_2$, $CaCO_3$, NaOH, KOH, NH_4OH, Na_2CO_3, $NaHCO_3$, K_2CO_3, $KHCO_3$, $(NH_4)_2CO_3$, NH_4HCO_3, i.e. with bases or alkaline salts.

The following examples are given to explain the invention and are not meant to restrict it.

Example 1

200.0 g of L-(+)-ibuprofen are mixed thoroughly with 80.0 g of 20% ammonia solution; incorporated into this mixture are then 100.0 g of finely powdered cellulose and 14.0 g of hydrolysed gelatine. After coarse sieving through a 3 mm mesh sieve follows drying at 50°C in a fluidised bed drier. After drying the granulate is beaten through a 0.8 mm sieve. Admixed as outer phase or as decompositi accelerator and lubricant are 40.0 g of maize starch, 7.0 g of cross-linked polyvidon and 3.0 g saccharose stearic acid ester S-370 F; then follows tabletting in the usual way.

Example 2

In a fluidised bed granulator 200.0 g of ibuprofen are mixed with 126.0 g of mannitol and 10.0 g of polyvidon and then sprayed with a granulation liquid consisting of 28.5 g of $Ca(OH)_2$ and 100.0 g of water and with 42.5 g of ammonia solution 10%. At the same time the material is dried with hot air of 70-120°C. As soon as the granulate has reached the prescribed degree of dryness it is blown cold with unheated air, beaten through a 1 mm sieve and, after adding 30.0 g of wheat starch, 7.0 g of Ac-Di-Sol (cross-linked sodium-carboxymethyl cellulose) and 3.0 g of calcium archinate as disintegrant and lubricant, is tabletted in the usual way.

Example 3

200.0 g of L-(+)-ibuprofen are mixed with 28.5 g of $Ca(OH)_2$ and then wetted with 70.0 g of 20% potassium hydroxide solution. After even wetting are added 80.0 g of maize starch and about 80.0 to 100.0 g of water are kneaded in in portions until a moist-plastic mass that can be granulated has come about. This is wet-granulated through a 3 mm sieve and dried at 40°C in a fluidised bed drier. When the desired degree of dryness has been obtained the material is put through a 1 mm sieve. Finally 25.0 g of maize starch and 10.0 g of talcum coated with 10% stearic acid are admixed as the outer phase before tabletting takes place.

Example 4

75.0 g of glycine are dissolved in 180.0 g of water and in this solution are dissolved under stirring and heating 38.0 g of $Ca(OH)_2$. Produced with this solution is a mixture of 200.0 g of ibuprofen, 50.0 g of microcrystalline cellulose and 10.0 of hydrolysed gelatine; if required a little water is added until a moist-plastic
Column 7 mass has been obtained that can be granulated. This mass is wet-granulated using a 3 mm sieve. After drying at 60°C and sieving through a 0.8 mm sieve are added as decomposition accelerator and lubricant 30.0 g of wheat starch, 7.0 g of cross-linked polyvidon and 3.0 g of calcium arachinate before tabletting takes place in the usual way.

Example 5

75.0 g of glycine are dissolved in 130 to 150.0 g of water and 70.0 g of 20% potassium hydroxide solution are added. Dissolved in this solution under heating are 28.5 g of $Ca(OH)_2$. Sprayed with this solution in a fluidised bed granulator is a mixture of 200.0 g of L-(+)-ibuprofen and 100.0 g of microcrystalline cellulose and then dried with hot air of 60°C. As soon as the prescribed degree of dryness has been obtained it is blown cold with unheated air, the granulate is taken from the device, sieved, the usual disintegrants and lubricants are admixed and then follows tabletting.

Patent Claims

1. Preparation with improved tablettability containing ibuprofen and/or S-(+)-ibuprofen as well as customary additives and/or vehicles the charcteristic of which is that it contains the calcium ibuprofen salt and/or the calcium S-(+)-ibuprofen salt.

2. Preparation in accordance with Claim 1 the characteristic of which is that it contains additionally at least one compound of the group sodium-, potassium-, ammonium-S-(+)-ibuprofen salt, ibuprofen and S-(+)-ibuprofen.

3. Preparation in accordance with Claim 2 the characteristic of which is that it contains
a) 50 to 100%w calcium ibuprofen salt and/or calcium S-(+)-ibuprofen salt,

b) 0 to 50%w sodium-, potassium-, ammonium ibuprofen salt, sodium-, potassium-, ammonium S-(+)-ibuprofen salt, ibuprofen, S-(+)-ibuprofen, related to the mix of the components of group a) and group b).

4. Preparation in accordance with one of the Claims 1, 2 or 3 the characteristic of which is that it contains 15 to 60% of the equivalent weight, related to the active substance ibuprofen and/or S-(+)-ibuprofen, of a neutral or acid amino acid.

5. Preparation in accordance with Claim 4 the characteristic of which is that as the amino acid it contains glycine, alanine, valine, aspartic acid, glutaminic acid, proline or hydroxyproline.

6. Preparation in accordance with at least one of the Claims 1 to 5 the characteristic of which is that it is in a form suitable for oral intake.

7. Preparation in accordance with Claim 6 the characteristic of which is that it is in form of tablets, pills, coated tablets, capsules, granulate or in form of tablets, pills, coated tablets, capsules or granulate with retard effect.

8.Process for the production of the preparation in accordance with at least one of the Claims 1 to 7 the characteristic of which is that ibuprofen or S-(+)-ibuprofen or a mixture of these, possibly with incorporated additives and/or vehicles, is treated with a solution of calcium oxide, calcium hydroxide, calcium carbonate, sodium hydroxide, potassium hydroxide, ammonium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, ammonium carbonate or ammonium bicarbonate or a suspension of these, possibly with added additives or vehicles, that the mixture obtained is granulated in a way known as such, is dried where applicable and, possibly after adding further adjuncts and/or vehicles, in a way known as such, is made into a form that is suitable for oral intake.

Column 8

9. Process in accordance with Claim 8 the characteristic of which is that the quantity of calcium, alkali or ammonium compound used amounts to 25 to 110 times the equivalent quantity, related to the active substance.

10. Process in accordance with one of the Claims 8 or 9 the characteristic of which is that at any stage of the process is added, in solid form, as a solution or as a suspension, a neutral or acid amino acid in a quantity amounting to 50 %w in relation to the active substance.

11. Process in accordance with Claim 10 the characteristic of which is that the lower amino acid is added to the granulation liquid.

12. Process in accordance with at least one of the Claims 8 to 11 the characteristic of which is that what is produced as a form suitable for oral intake are tablets, pills, coated tablets, capsules, a granulate or tablets, pills, coated tablets, capsules or a granulate with retard effect.